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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/524,051 | 02/08/2005 | Lieven Meerpoel | JAB1742USPCT | 6822 |
| 27777 7590 11/23/2007 PHILIP S. JOHNSON JOHNSON & JOHNSON ONE JOHNSON & JOHNSON PLAZA NEW BRUNSWICK, NJ 08933-7003 | | | EXAMINER O DELL, DAVID K | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|-------------------------------|---------------------------------|--|
| Office Action Summary | Application No. 10/524,051 | Applicant(s) MEERPOEL ET AL. | |
| | Examiner David K. O'Dell | Art Unit 1625 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 February 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 and 10-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 and 10-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>8 February 2005</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-8, 10-21 are pending in the current application.

Priority

2. This application is a 371 of PCT/EP03/08694 filed 08/05/2003 and claims priority to European application 02078309.8 filed 08/12/2002. The bibliographic data sheet in this application file has been corrected by the examiner to show the filing date of European application 02078309.8 as 08/12/2002, which had been previously recorded as 08/17/2002.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following language results in a deficiency under 112 2nd paragraph:

“X1 and X2 are either both carbon, or when one of X1 or X2 is nitrogen, than the other X1 or X2 is carbon; X3 is carbon, or nitrogen provided that only one of X1 or X2 is nitrogen;”

It is unclear what X1 and X2 are. While they are defined as carbon, the limitation “when one of X1 or X2 is nitrogen”, lacks antecedent basis since X1 and X2 have been defined as only carbon.

4. Claims 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to treating “a disorder caused by an excess of very low density lipoproteins (VLDL) or low density lipoproteins (LDL)”. It is unclear what diseases this

Art Unit: 1625

is meant to encompass. The metes and bound of this language makes the scope of the claims unascertainable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds it does not reasonably provide enablement for the scope of compounds bearing the extensive list of substituents. The compounds that are enabled are as follows:

R1 -R4 are enabled as written for pyridine and benzene (where X1-X3 is carbon or one of X1-X3 is N), but with respect to certain definitions of X1, X2, and X3, namely where X2 and X3 are N and X1 is carbon and where X1 is N and X3 is N and X2 is C, the claims are not enabled for any compounds. With respect to (C=O)-Y-R5 only benzyl or alkyl esters and amides are enabled not the 14 heteroaryl groups claimed.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement

Art Unit: 1625

and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

- (A) The breadth of the claims;*
- (B) The nature of the invention;*
- (C) The state of the prior art;*
- (D) The level of one of ordinary skill;*
- (E) The level of predictability in the art;*
- (F) The amount of direction provided by the inventor;*
- (G) The existence of working examples; and*
- (H) The quantity of experimentation needed to make or use the invention*

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a long list of , optionally substituted phenyl and 14 heteroaryl groups bearing multiple substitutions **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should have activity at MTP/apoB. **(D) The level of one of ordinary skill:** One of ordinary skill is a practicing organic/medicinal chemist. **(C) The state of the prior art:** **(E) The level of predictability in the art:** **(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** Each one of the factors (C, E-H) will be discussed in light of the scientific literature when such a factor is being directly pointed to a large capital letter referring to the aforementioned Wands factor will be placed directly after such a remark or explication. The examiner will first consider the Markush structure I of claim 1, and discuss the limitations inherent to the chemistry required to prepare the compounds as well as the paucity of available starting materials. These materials are prepared by SN_{Ar} reaction by a piperidine on a para-Fluoro-nitrobenzene, followed by nitro reduction and acylation with a biphenyl carboxylic acid. This sequence no doubt works quite well for the phenyl (the working example) and

Art Unit: 1625

pyridine compounds, and these are surely commercial or easily synthesizable, however for the remainder of the compounds claimed by the identity of X1, X2, & X3, no such fluoronitrodiazine starting materials are known. The examiner conducted a search that reveals only a single known diazine bearing a fluoro and nitro group, and it does not support the claimed invention however (it bears a carboxylate). The examiner has attached these results to the PTO-892 as (Known fluoronitrodiazines). Most disturbingly the species of the instant specification require these materials. Where can one purchase or find the directions to prepare the fluoronitrodiazines needed for the scope of the claims? As per MPEP:

A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in *In re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In *re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the specification is enabling to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed*, (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the

Art Unit: 1625

situation here. Rather we find no direction as to how the many required starting materials with are to be obtained. Where may the directions to prepare or buy them be found? (F)

In re Howarth, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-yl-p-nitrophenyl-2-dichloracetamido-propane-1,3-diol not enabled because of failure to describe source or method of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula).

The limitations of synthetic chemistry is readily apparent as stated in the preface to a recent treatise:

““Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team

Art Unit: 1625

of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) [preface].....even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]..... As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]..... As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. [8].....Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, specially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9].....” Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15. (E)

Many of the compounds currently under the Markush claim could not exist but would self-polymerize instantaneously if prepared as stated by Dorwald *ibid.* pg. 41 “It goes without saying that a compound will decompose or oligomerize if it contains functional groups which can react with each other. Because intramolecular reactions often proceed at much higher rates than their intermolecular variants, functional group incompatibilities may arise unexpectedly, involving groups which would not react intermolecularly...” A notable example is compounds bearing multiple amino groups and alkyl iodides. (C & E)

While these chemical limitations are significant, perhaps more significantly are the limitations of activity at MTP/apoB. We have not been given any information in regard to the molecular determinants of receptor affinity for the compounds of the instant case for “heteroaryls”. In fact only a very limited amount of information is given for a very few compounds that do not have R5 as “heteroaryl”. In the case of the MTP assay, we are given directions on how to conduct an assay and no actual performance of the compounds in the assay has been revealed. In this case these claimed compounds with “heteroaryl” on R5 bear no structural resemblance to one another and even if they did the situation is far from clear that they would have the desired activity. As one reviewer stated, Martin, Yvonne C. et. al. “Do Structurally Similar Molecules Have Similar Biological Activity?” *Journal of Medicinal Chemistry* 2002, 45, 4350-4358:

“..... compounds that look very similar to a chemist sometimes bind in very different orientations in the protein active site, bind to a different conformation of a protein, or bind to a different protein altogether.¹⁵ In fact, such observations are why medicinal chemists need to make so many compounds to optimize the biological activity of a structural class, even when they are designing to a biological target of known structure...(pg. 4536 column 2, line 9).....This work also shows that the biological similarity is not so strong as has previously been assumed. For example, at ≥ 0.85 Tanimoto similarity in Daylight fingerprints,

Art Unit: 1625

only 30% of compounds similar to an active are themselves active.”(conclusions)

The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation.

6. Claims 20-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using certain compounds to treat hyperlipidemia, obesity, atherosclerosis, or type II diabetes, it does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue.” These factors include, but are not limited to the following:

- (A) **The breadth of the claims;**
- (B) **The nature of the invention;**
- (C) **The state of the prior art;**
- (D) **The level of one of ordinary skill;**
- (E) **The level of predictability in the art;**
- (F) **The amount of direction provided by the inventor;**
- (G) **The existence of working examples; and**
- (H) **The quantity of experimentation needed to make or use the invention**

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Art Unit: 1625

The basis of this rejection is the same as that above in this action at 5. The factors outlined in *In Re Wands* mentioned above apply here. It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-7, 12-17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-7 of copending Application No. 11/558,655. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to the same compounds., in particular where in the '655 application X1 is N, Z is a-2.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Art Unit: 1625

8. Claims 1-8, 10-17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-10 of copending Application No. 11/854,632. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to Markush claims that overlap in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Claims 1-8, 10-21 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-24, 26-31 of copending Application No. 11/551,288. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '288 application is drawn to compounds and methods embraced by the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. Claims 1-8, 10-21 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-16 18 of copending Application No. 11/928,942. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to Markush claims that overlap in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 1-7, 12-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-7 of U. S. patent 7,304,167. Although the

Art Unit: 1625

conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to the same compounds.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

R. Desai
RITA DESAI
PRIMARY EXAMINER
11/20/07